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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,241	12/21/2001	L. Kathryn Durham	PC11028AGPR	6632

7590 02/13/2004

Gregg C. Benson
Pfizer Inc.
Patent Department, MS 4159
Eastern Point Road
Groton, CT 06340

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,241	DURHAM ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *6-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/28/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

Election/Restrictions

Applicant's arguments filed 11/21/03 have been fully considered but they are not persuasive. Applicant's election with traverse of Group I, claims 1-5 and 34-37 and the polymorphism of insertion 307 is acknowledged. The traversal is on the ground(s) that the examiner could, without undue burden on his time or searching efforts, search and examine all claims simultaneously and that the present restriction requirement requires the applicant to pay over 150,000 in filing fees. While applicant's arguments are acknowledged, it is maintained however, that the *Official Gazette* and notices posted on the PTO website have included guidance "to include up to 10 nucleotide sequences per application." The examiner retains his/her discretion in the inclusion of "up to 10 sequences." It is further maintained that the examiner adhered to the PTO policy concerning restriction practice as defined in *35 U.S.C. 121*, "if two or more independent and distinct inventions are claimed in one application, the commissioner may require the application to be restricted to one of the inventions." The examiner maintains that the inventions are distinct, each from the other because of the following reasons:

These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Thus the claims read on a multitude of groupings of polymorphisms, each of which is separate and distinct one

from another because they contain nucleic acid sequences that are structurally separate from one another. The search and examination of all possible groups would pose an enormous burden on the examiner and on the PTO search resources. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter since all of the polymorphisms would require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore the restriction is deemed proper and is made final.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of a U.S. provisional Application 60/258,072 filed December 22, 2000, is granted.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code(Pg. 31, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Drawings

Applicant's drawings submitted on 6/4/2002 are objected to for the following reasons.

A. Figure 6 is objected to for its recitation of "Insertion 347", as it is assumed by the examiner that instead it should read "Insertion 307". Furthermore the correction of the figure's recitation of "REZI" as opposed to "Rsa I" and C3797T and G797A instead of C3707T and G707A respectively is also required.

B. Figure 9's recitation of "G/Q" on the x-axis label is also objected to and requires appropriate correction.

C. The descriptions for and Figure 10 and Figure 11 are objected to as there are two descriptions of each figure, on page 12 and a different one under table 3 in the examples section on pages 49-50. These two descriptions should be consolidated and placed in the section entitled "Brief Description of the Drawings".

Claim Objections

A. Claim recitation of "A method for determining a whether a subject" is grammatically incorrect, appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-5 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-5 and 34-37 are indefinite over the recitation of "insertion (307)" as the actual placement of the "insertion (307)" is not defined by the claim, the specification does not provide a definition and an exact position with the corresponding sequence that results from an "insertion (307)". There is no fixed definition in the art for what constitutes the DNA sequence having at least one CETP allele selected from the group consisting of "insertion (307)". In referencing the specification for a definition on page 28, while the first two flanking sequences are present in the Figure 3 of SEQ ID NO:3, the third sequence is not present and it is therefore unclear how or what an "(insertion 307)" would represent in the CETP gene. It is further unclear if "insertion (307)" represents the occurrence of an insertion or not, allele 1 or allele 2, a mutant or a wild-type, and what any of these sequences would be. Applicant must amend the claims to clarify the exact variant and its exact location in the proper SEQ ID NO that is being claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-5 are broadly drawn to a method for determining whether any subject has any modification of susceptibility to any cardiovascular disease comprising detecting in any nucleic acid sample any at least one CETP allele of "insertion (307)" wherein this allele is associated with any modified level of CETP activity and further wherein said allele is an "insertion (307) allele 2" wherein detection of said allele indicates that the subject has a decreased predisposition to cardiovascular disease. The claims 34-37 are broadly drawn to a method of identifying any subject suffering from any cardiovascular disorder that would be responsive to treatment with any at least one cardiovascular disorder therapeutic, comprising: detecting in a any nucleic acid sample from a subject at least one CETP allele of "insertion (307)" wherein said CETP allele is associated with any modified level of CETP activity. However, as will be further discussed, the specification and prior art lack support for the enablement of these methods as claimed. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites in Table 1, 2 patterns exhibited by 2 CETP Haplotypes(Pg. 32). The specification discloses that haplotype pattern 1 is associated with higher CETP levels and lower HDL levels, while haplotype pattern 2 is associated with lower CETP levels and higher

HDL levels. The specification further states that Haplotype 1 is indicative of risk factors commonly associated with the development of cardiovascular disorders. In Table 2, the specification discloses the strong linkage disequilibrium that exists between the Taq1, MSP1, Rsa1, and the homozygous wild-type (G/G) at SNP 565 (or equivalently no insertion at 307) SNP 565 when the "112 haplotype" is present, which is to say that each polymorphic site is wild-type(Pg. 48). The specification continues to assert that the presence of a single "C" allele at SNP 565(or a single insertion at 307) is strongly associated with a "221 haplotype" which is to say that each of the Taq1, MSP1, Rsa1 sites are mutant. Table 3 displays the statistical analysis of genotype/phenotype correlations. The table teaches that Taq1 and Msp1without asserting whether these two are wild-type or mutant, each by themselves are associated with only CETP concentration(not an increased or decreased CETP concentration). The table further asserts that the SNP 565, again without a distinction of wild-type or mutant, is correlated to HDL(not an increased or decreased amount of HDL). Lastly the table teaches that a certain "number of 1121 haplotypes" and "number of 2212 haplotypes" take on different phenotypes as previously predicted when they are assembled together(for example: Taq1(2) and Msp 1(2) become correlated with HDL instead of CETP. With respect to claims 34-37, the specification on page 43 teaches that in patients that have a cardiovascular disorder and an allele of pattern 1, pharmaceuticals that are CETP antagonists are likely to have a beneficial effect. Furthermore, "patients with pattern 2 presenting with cardiovascular disorder will benefit less from a CETP antagonist because the CETP levels are already low in these patients"(pg. 43). However the specification also acknowledges on page 7 that "many variables in the patient pool are controlled for, but effects of genetic variability are no typically assessed...a drug may be statistically ineffective when examined in a diverse pool of patients and yet be highly effective for a select group of patients with particular genetic characteristics"(pg. 7). Furthermore and with respect to claims 1-5 and 34-37, on page 9 of the specification applicants presume that "for the purposes of

diagnostic and prognostic assays for a particular disease, detection of a polymorphic allele associated with that disease can be utilized without consideration of whether the polymorphism is directly involved in the etiology of the disease".

However, implicit in the above assumption is the applicant's retention of a predictable disease-causing loci whose use is well known in the art to consistently, accurately, and without qualification predict a disease. The specification lacks any teaching of such a well-known disease-causing loci and furthermore any teaching of a diverse, sampled population in which their results are founded(On page 47 the specification teaches only that 46 non-descript patients were sampled). The prior art teaches that much unpredictability exists in correlating the Taq1B cholesteryl ester transfer protein (CETP) gene polymorphism (B1B2), CETP mass and any disorder. On page 6 of the specification, several references are pointed to for their teaching of "Taq 1, Msp1, and Rsa 1 polymorphisms" and their association with modification in CETP and HDL levels. One of these references, Kuivenhoven et al.(Arteriosclerosis, Thrombosis & Vasc. Biol. 17:560-8 (1997)) does in fact teach that the "B1-M1-R2 haplotype was over-represented in the low HDL cholesterol group, whereas the B2-M2-R1 haplotype was over-represented in the high HDL cholesterol group"(Pg. 566 right) and further in homozygous subjects for B1-M1-R2 and B2-M2-R1 the reference teaches that the former group exhibited higher CETP concentrations and lower HDL cholesterol than did homozygotes for B2-M2-R1. However, the reference also teaches going to great lengths to select a proper sample population with which they were able to obtain these results. Kuivenhoven teaches a population consisting of "healthy men with low, median, and high plasma HDL cholesterol...matched for lifestyle parameters and clinical features that affect HDL cholesterol levels"(Pg. 564 right). The reference further teaches that "we speculate, therefore, that the role of the CETP gene in determining high HDL

cholesterol in Japanese and whites differs as a result of the absence of frequent functional CETP mutations in whites"(Pg. 565). The reference also teaches the uncertainty involved in this method in their realization that "Tato et al. recently reported less CAD in patients with low HDL and high CETP activity than in subjects with low HDL and normal CETP activity. In addition, others indicated that CETP activity might inhibit the progression of atherosclerotic lesions in hypertriglyceridemic mice. These findings clearly illustrate our incomplete knowledge of the exact role of CETP in atherosclerosis and the need of further in-depth investigations"(566). Another reference teaches that in a population of 406 NIDDM subjects, "we found the Taq1B polymorphism of the CETP gene to have an impact on the HDL-C(cholesterol) concentrations in male subjects only, females displaying equally high concentrations independent of genotype"(Durlach et al. JCE & M 1999). The reference then teaches that "anterior studies have not explored the possibility for a sex-difference in response to polymorphism, but this observation adds to the already large corpus of data indicating that the relationships between HDL cholesterol and CETP activity is not a direct one"(pg. 3658). Another cited prior art reference teaches that "most study groups published so far consist only of men, but a difference between the sexes has been found earlier with the TaqIB and R451Q polymorphism of the CETP gene"(Kakko et al. European Journal of Clinical Investigation, 2000, page 24). The reference continues to teach that "the actual mutations in linkage disequilibrium with the Taq IB and I405V polymorphisms are likely to be different and their effects on reverse cholesterol transport might not be identical"(Kakko et al. Pg. 24). Although the above references also point to the unpredictability of identifying any subject suffering from a cardiovascular disorder that would be responsive to treatment with any at least one therapeutic by detecting either the presence or

absence of an insertion 307 that is eventually linked to the TaqIB polymorphism of the CETP gene, Altshuler et al. further corroborate the unpredictable nature of the art. After referencing the Kuivenhoven et al. of New England Journal of Medicine 1998, the reference cautions the association of allelic variants with common diseases. Altshuler et al. teach that before examining issues of clinical utility and biologic plausibility, "we must first convince ourselves that putative associations are real"(Pg. 1626 NEJM, May 28, 1998). The reference continues to point out that in similar studies involving linkage between an allele and a disease, while initially in a limited population a "strong association was reported, further investigation failed to demonstrate linkage and revealed that the frequency of the allele varies widely between ethnic groups"(Altshuler et al. pg. 1626).

The post filing date art further confirms the unpredictability of this area. Bauerfeind et al. teach SNP haplotypes in the CETP gene and that while "the associations were robust for men, but not for women" their "data suggest an interaction between gender and genetic variation within the CETP gene"(Bauerfeind et al. Human Heredity, 2002; 54: 166-173). Lastly an article entitled: *Haplotype analyses of the CETP gene promoter: a clue to an unsolved mystery of Taq1B polymorphism* teaches that "the TaqIB polymorphism may not play a direct role in determining plasma CETP concentrations, whereas the haplotype consisting of –2505 may provide a starting point for understanding the complex genetic background of variability in CETP concentrations and HDL metabolism, and therefore the risk of coronary artery disease"(Lu et al, J Mol Med 2003). Clearly the art adds to the great unpredictability in the use of the presently claimed invention.

It should further be noted that considering the correlation of a SNP with a disease, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Determining how to use the claimed polynucleotides as asserted by applicant, for example for the diagnosis of disease and identifying a subject that would be responsive to a particular treatment, requires the knowledge of unpredictable and potentially non-existent associations between the polymorphism and cardiovascular disease in all subjects. Even if the elected polymorphism is in some way associated with cardiovascular disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which component of the disease or how the polymorphism is associated and therefore also, how to identify any subject that would be responsive to a particular treatment because of a detected allele. That is, it is unpredictable as to whether the presence of a particular allele of the polymorphism would confer a higher or lower likelihood of having the disease in a particular population of people and furthermore if the linkage association would even still remain in different populations. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a cardiovascular disease associated with the polymorphism.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to every subject, every modified susceptibility, to any component of cardiovascular disease by detecting any nucleic acid with any at least one CETP allele of "insertion (307)" wherein said allele is associated with any modified level of CETP activity. In order to use the claimed invention as asserted by the specification, one would have to establish a reliable and consistent relationship between the insertion 307 and some cardiovascular disease state, some disease treatment method, or other relevant phenotypic state. In order to obtain the type of information necessary to practice

the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's insertion 307 would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the polymorphism and any cardiovascular disease or condition. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples that provide direction in how to use this method with any population and to obtain the same results as they did with their 46 non-descript study participants.

Guidance in the Specification.

The specification provides no evidence that the disclosed method would be able to determine susceptibility to cardiovascular disease through the detection of the insertion 307 CETP allele. Not only does the specification lack teachings that would predictably correlate this allele in every population, but also lacks teaching that the linkage disequilibrium would be maintained between insertion 307, SNP 565, and the Taq1, Msp1 and Rsa1 alleles that have been shown to have a limited association to HDL and CETP levels. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that if an

insertion 307 is detected, a susceptibility to cardiovascular disease must necessarily exist because of the insertion's linkage to the SNP 565, and the Taq1, Msp1 and Rsa1 alleles. Even if, arguendo, the insertion 307 would forever be linked to these other polymorphisms, the retention of Taq1B's association with HDL and CETP concentration is highly unpredictable as was seen above.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where methods using SNPs as disease-causing loci depends upon numerous known and unknown parameters such as the genetic background, environmental stimuli, and varying metabolic variables, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provide insufficient guidance to overcome the art recognized problems in the use of an ,insertion 307, to determine a susceptibility to cardiovascular disease. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

35 U.S.C. 112, Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

The specification discloses SEQ ID NO: 3 that corresponds to the Human cholesteryl ester transfer protein (CETP) gene, exons 12-14, accession number M32997. Claims 1-5 and 34-37 are directed to encompass a method wherein a CETP allele is selected that consists of "insertion (307)". While on page 28 of the specification it is taught that the polymorphisms is characterized by a 15 bp insertion in intron 12 of the CETP gene and the insertion occurs at nucleotides 643-657, the flanking sequences provided do not reveal the actual structure of the insertion 307. While a NCBI blast of the first two sequences GAATGGAGGG-CTGCCAGGAAGAAGG- aligns them with the sequence of M32997, the third sequence's relevance remains unclear as it is not present in M32997. The third sequence cannot be the inserted sequence as it is only 10 nt long, but it is not found as a flanking sequence either. As a result it is unclear what resulting structure will occur following the insertion at 307. A review of the full content of the specification indicates that the sequence of insertion 307 of SEQ ID NO: 3 and all aforementioned variations, are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:3, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The named ORF is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for isolating and characterizing cDNA sequences from *E. grandis*, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe *E. grandis* cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the specification does, does not necessarily describe the cDNA itself. No sequence

information indicating which nucleotides constitute *E. grandis* cDNA appears in the application. Accordingly, the specification does not provide a written description of the invention of claims 1, 4, and 6-15.

Therefore, none of the sequences encompassed by the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (571)272-0748. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Jeffrey Fredman, can be reached at (571)272-0742. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782. The official fax number is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (571)272-0518.

Sally Sakelaris
2/6/2004

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600